Phase II Trial of Temozolomide and Irinotecan as Second-Line Treatment for Advanced Non–small Cell Lung Cancer

Nicholas W. Choong, MD, Ann M. Mauer, MD,*† Philip C. Hoffman, MD,*†*
Charles M. Rudin, MD, PhD,‡ Jerome D. Winegarden, III, MD,§
J. Lee Villano, MD, PhD, Mark Kozloff, MD,‖ James L. Wade, III, MD,¶ David F. Sciortino, MD,#*
Livia Szeto, RN, and Everett E. Vokes, MD*†*

Background: This study was performed to evaluate the tolerability and efficacy of temozolomide and irinotecan as a second-line regimen in recurrent/metastatic non–small cell lung cancer (NSCLC).

Methods: Patients with recurrent/metastatic NSCLC, including those with treated brain metastases, following one prior platinum-based regimen received temozolomide 75 mg/m^2 daily on days 1 through 15 and irinotecan 100 mg/m^2 on days 8 and 15 every 21 days.

Results: The authors treated 46 patients, of whom more that 90% had a performance status of 0 or 1. Four patients (8.7%) attained partial response and 17 (37.0%) had disease stabilization as their best response. The median time to progression was 1.8 months, median overall survival was 9.8 months, and 1-year overall survival was 34%. Grade 1/2 fatigue (63%), anemia (61%), nausea (52%), and diarrhea (44%) were the most common toxicities. Grade 3/4 leukopenia and diarrhea were each observed in 9% of patients. One unexpected death occurred, possibly related to the regimen.

Conclusion: Second-line treatment with temozolomide and irinotecan showed tolerable toxicities. The response rates, median survival times, and 1-year survival rates were comparable to other active NSCLC agents.

Key Words: Non–small cell lung cancer, Metastasis, Temozolomide, Irinotecan.

(*J Thorac Oncol.* 2006;1: 245–251)

*Section of Hematology-Oncology and Phase II Network, University of Chicago Medical Center, †University of Chicago Cancer Research Center, Chicago, Illinois; ‡Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; §Ann Arbor Hematology Oncology Associates, St. Joseph Mercy Cancer Center, Ypsilanti, Michigan; ‖Ingalls Hospital, Harvey, Illinois; ¶Decatur Memorial Hospital, Decatur, Illinois; and #Fort Wayne Oncology-Hematology, Fort Wayne, Indiana.

Presented at the 11th World Conference on Lung Cancer, in Barcelona, Spain, July 3–6, 2005. Address for correspondence: Everett E. Vokes, MD, Section of Hematology-Oncology, University of Chicago Medical Center, MC 2115, 5841 S. Maryland Avenue, Chicago, IL 60615; email: evokes@medicine.bsd.uchicago.edu.

ISSN: 1556-0864/06/0103-0245

Lung cancer is the leading cause of cancer mortality in the United States. Approximately 172,000 new lung cancer cases and 164,000 deaths were expected in 2005.[1] Worldwide, there were 10 million newly diagnosed lung cancers in the year 2000.[2] Non–small cell lung cancer (NSCLC) accounts for the majority of lung cancers, and approximately 70 to 80% of patients with NSCLC present with locally advanced or metastatic disease.[1] Almost all patients with locally advanced or metastatic disease will relapse within a short time after initial treatment. U.S. Food and Drug Administration–approved second-line agents—docetaxel,[3] pemetrexed,[4] and erlotinib[5]—produce response rates of approximately 10%, with a median survival of 8 months. Furthermore, 30 to 40% of NSCLC patients have brain metastasis during the course of their disease, resulting in significant morbidity.[6,7] Brain metastases are believed to occur because of the inability of most chemotherapy agents to cross the blood-brain barrier.

Temozolomide is an orally administered prodrug that is converted spontaneously to the active alkylating agent monomethyl triazenoimidazole carboxamide at physiologic pH.[8] Temozolomide is able to cross the blood-brain barrier and reaches therapeutic concentrations in the cerebrospinal fluid.[9] Currently, temozolomide is standard therapy in patients with refractory anaplastic astrocytomas.[10,11] It is also effective in primary brain tumors when given concurrently with radiation therapy in the first-line setting.[12] Monotherapy temozolomide has activity against brain metastasis from a variety of solid tumors including NSCLC,[13,14] and the effect of radiotherapy is enhanced by temozolomide.[12,15,16] Furthermore, temozolomide has demonstrated some single-agent activity in the second-line setting in NSCLC.[17]

Temozolomide exerts its effect by methylating the O^6-position in the guanine residue, producing O^6-methylguanine, which is paired to thymine. This abnormal pair is recognized by the mismatch repair system, and in the process of removing the methylated guanine residue, apoptosis occurs.[18] Apart from the mismatch repair system, the O^6-methylguanine residue can be removed by an intranuclear enzyme called O^6-methylguanine-DNA-methyltransferase (MGMT).[19,20] Temozolomide resistance has been correlated with high levels of MGMT.[19–21] Overcoming such resistance may increase the activity of temozolomide. It has been shown

that the level of MGMT decreases progressively with each dose of temozolomide (as DNA damage is repaired).[22] Thus, an extended administration schedule of temozolomide should result in a cumulative and sustained depletion of MGMT. When temozolomide was administered in recurrent glioma patients for 6 to 7 weeks at 75 mg/m^2 per day, the regimen was well tolerated and the major toxicity was reversible marrow suppression (neutropenia and thrombocytopenia).[23] This regimen resulted in a twofold higher drug exposure over 4 weeks (2100 versus 1000 mg/m^2 over 4 weeks) compared with the conventional dosing of 150 to 200 mg/m^2 per day for 5 days every 28 days. Furthermore, with a response rate of 33% in recurrent glioma patients, the extended dosing schedule compared favorably with the conventional schedule.[24] Other groups have confirmed that temozolomide at 75 to 100 mg/m^2 per day for 3 weeks repeated every 4 weeks was well tolerated and resulted in marked reduction in MGMT levels.[25,26]

In an attempt to increase the activity of temozolomide, we combined it with irinotecan using the extended dosing schedule of temozolomide. Irinotecan, a derivative from the *Camptotheca acuminata* tree, inhibits DNA and RNA synthesis through DNA topoisomerase I inhibition.[27] Irinotecan is a standard chemotherapy in colorectal cancer.[28] In small-cell lung cancer, the combination of cisplatin and irinotecan has demonstrated significant efficacy.[29] Irinotecan in combination with a platinum agent as first-line therapy in NSCLC is efficacious and well tolerated.[30,31] In the second-line setting, irinotecan in combination with other cytotoxic chemotherapies has also demonstrated activity in exploratory trials.[32,33]

Irinotecan has synergistic activity when combined with alkylating agents[34] and with temozolomide specifically.[35,36] The formation of O^6-methylguanine by temozolomide results in recruitment of topoisomerase I[37]. This increases the chances of a topoisomerase I inhibitor such as irinotecan to bind and stabilize the cleavage complex, leading to further DNA damage. The combination of temozolomide and irinotecan was well tolerated in phase I dose-escalation studies.[38] In patients with recurrent gliomas, the combination demonstrated favorable response rates and low toxicity rates, with grade 4 leukopenia and thrombocytopenia occurring in 3% and 6% of patients, respectively, and no nonhematologic grade 3 or 4 toxicities were seen.[39] With enhanced activity demonstrated in preclinical studies, nonoverlapping toxicities, and encouraging clinical results, we conducted a multicenter phase II trial combining temozolomide and irinotecan as second-line therapy in advanced NSCLC.

PATIENTS AND METHODS

Study Subjects

Patients with histologically or cytologically confirmed NSCLC with disease progression after one prior platinum-based chemotherapy regimen were included in the study. All patients were older than 18 years; had an Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate hematologic (white blood cell count $\geq$ 3000 cells/μl, absolute neutrophil count $\geq$ 1500 cells/μl, platelet count $\geq$ 100,000 cells/μl), hepatic (total bilirubin within normal institutional limits, serum transaminases $\leq$ 2.5 times the institutional upper limit of normal), and renal (creatinine clearance $\geq$ 60 ml/min) function. All patients were also required to have at least one measurable lesion on computed tomographic scanning. Patients with treated (radiation or surgery) or asymptomatic brain metastasis were eligible for the study, provided they were on a stable or downward tapering dose of steroids.

Patients on phenytoin were excluded because phenytoin up-regulates irinotecan metabolism, leading to lower plasma concentrations of irinotecan.[40] At least 4 weeks had to have elapsed from completion of the last cycle of chemotherapy before commencing the trial. Other exclusion criteria were prior treatment with temozolomide or irinotecan; uncontrolled intercurrent illness including but not limited to active infections, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness that would limit compliance with the study requirements; pregnancy; and immunodeficiency syndromes.

Study Design

The primary objective of this multicenter single-arm phase II trial was to assess the therapeutic activity of temozolomide and irinotecan in NSCLC as second-line therapy. The primary endpoint was overall response rate. Secondary endpoints were survival, time to disease progression, and toxicity.

The accrual plan for the study was to enroll the first six patients at the University of Chicago Medical Center at the initial dose level of temozolomide administered orally, 75 mg/m^2 daily on days 1 through 15, and irinotecan administered intravenously, 100 mg/m^2 on days 8 and 15 of a 21-day cycle. After the first six patients developed no unexpected toxicities, subsequent patients were treated with the same doses and schedule.

Patients were instructed to take temozolomide at bedtime after a 2-hour fast and to continue fasting for at least 1 hour after taking temozolomide. Patients recorded the exact time and dose temozolomide was taken on a case report form. Irinotecan was administered in the outpatient setting by intravenous infusion over 90 minutes in 250 ml of 5% dextrose.

Baseline and Follow-Up Assessment

Baseline assessments included complete medical history, physical examination, complete blood count, and serum complete metabolic panel. Because temozolomide is associated with an increased risk of *Pneumocystis* pneumonia,[41] patients on corticosteroids received trimethoprim/sulfamethoxazole 160/800 mg administered orally twice daily every Saturday and Sunday as prophylaxis. Patients were assessed for tumor response after every two cycles. Response and progression were evaluated using the Response Evaluation Criteria in Solid Tumors committee criteria.

In patients showing disease stabilization or objective response, the regimen was repeated every 21 days to a maximum of six cycles. For all patients who achieved a partial response (PR) or a complete response, confirmation by

repeat assessments was required 6 weeks after the criteria for response was met. In the case of stable disease (SD), follow-up measurements had to meet the SD criteria after at least a 6-week interval.

The Common Terminology Criteria for Adverse Events of the National Cancer Institute (NCI) version 2.0 was used for toxicity assessment. Doses of chemotherapy were modified according to any hematologic and nonhematologic adverse effects.

Dose reductions for hematologic and nonhematologic toxicities except for diarrhea, alopecia, asthenia, nausea, and vomiting were as follows: grade 1 toxicity, no dose reduction; grade 2 toxicity, 25% dose reduction in temozolomide; grade 3 toxicity, 50% dose reduction in temozolomide; and grade 4 toxicity, 75% dose reduction in temozolomide. For grades 3 and 4 diarrhea, the dose of irinotecan was reduced by 25% and 50%, respectively.

Statistical Analysis

The null hypothesis, that the overall response rate is less than 10%, was tested and we estimated a response rate of 25% or greater for the combination of temozolomide and irinotecan to be sufficient to warrant further study. Using the Simon's two-stage study design, 18 patients were recruited during the first stage. If fewer than three responses were observed, the study would be terminated. Conversely, if three of more responses were observed, an additional 25 patients were recruited. The null hypothesis would be rejected if there were eight or more observed responses. With this design, the probability of falsely rejecting the null hypothesis is 0.05 (one-sided alpha) and the probability of correctly rejecting the null hypothesis if the true response rate of 25% is at least 0.80 (80% power). If the true response rate was only 10%, the probability of early termination was 73%.

Progression-free survival was calculated as the time from registration to the first observation of disease progression, relapse, or death, whichever came first. Survival time was defined as the time between registration and death. Survivorship was estimated as a function of time from registration using the Kaplan-Meier survivorship analysis. All observed toxicities were recorded and summarized using appropriate descriptive statistics.

RESULTS

Patient Characteristics

The trial was initiated in March of 2002, and the last patient was enrolled in December of 2004. The first six patients accrued tolerated the regimen well in the first cycle without requiring dose reduction. One patient required a 25% irinotecan dose reduction in cycle 2 as a result of grade 3 diarrhea. After determining that the regimen was well tolerated at the doses administered (temozolomide, orally, 75 mg/m^2 daily on days 1–15; and irinotecan, intravenously, 100 mg/m^2 on days 8 and 15 in a 21-day cycle), a total of 46 patients were enrolled onto the study at participating hospitals of the University of Chicago Phase II Network. The participating patient characteristics are listed in Table 1.

TABLE 1. Patient Baseline Demographics

Characteristics	Value (%)
No. of patients	46
Age (yr)	
Mean	60
Range	32–80
Male-to-female ratio	30/16
Race	
White	32 (69.6)
African American	10 (21.7)
Asian	4 (8.7)
Performance status (ECOG)	
0	17 (37.0)
1	26 (56.5)
2	3 (6.5)
Interval between prior platinum-based chemotherapy and initiation of trial (mo)	
Median	4
Range	1–28
Tumor histology	
Adenocarcinoma	26 (56.5)
Squamous-cell carcinoma	6 (13.0)
Large-cell carcinoma	6 (13.0)
Poorly differentiated carcinoma	8 (17.4)
Stage at diagnosis	
I	2 (4.3)
IIIA	4 (8.7)
IIIB	15 (32.6)
IV	25 (54.3)
Stage at enrollment	
IIIA	4 (8.7)
IIIB	16 (34.8)
IV	26 (56.5)
Site of metastasis	
Brain	9 (19.6)
Lymph node	34 (73.9)
Adrenal gland	11 (23.9)
Bone	15 (32.6)
Contralateral lung	6 (13.0)
Liver	3 (6.5)
No. of sites involved by metastasis	
1	23 (50.0)
2	15 (32.6)
≥3	8 (17.4)

ECOG, Eastern Cooperative Oncology Group.

The mean age was 60 years (range, 32–80 years). More than 90% of patient had an Eastern Cooperative Oncology Group performance status of 0 or 1. Adenocarcinoma was the most common histologic subtype. The majority of patients had stage IV metastatic disease at the time of enrollment and the rest had recurrent or refractory stage IIIA or IIIB disease. All patients were previously treated with a platinum-based chemotherapy regimen. Brain metastases were present in nine patients (19.6%). The median interval between the last dose of platinum-based chemotherapy and registration on the trial

was 4 months (range, 1–28 months). All patients with brain metastases had been treated with whole-brain radiation therapy and were clinically stable prior to starting the study.

Response and Survival

All patients were assessed for response and toxicity and were included in the survival analysis. A total of 136 cycles were administered, with a median number of two cycles per patient (Table 2). Twelve patients (26.1%) completed six cycles of treatment. Eleven patients (23.9%) received only one treatment cycle. Clinical disease progression accounted for nine patients discontinuing treatment after one cycle of irinotecan/temozolomide. In the nine patients who received only one cycle of irinotecan/temozolomide, two developed worsening pleural effusions, four developed worsening respiratory failure attributed to disease progression, two developed new bone metastasis, and one developed new supraclavicular lymphadenopathy. Two other patients discontinued therapy after one cycle as a result of severe diarrhea requiring hospitalization. One episode of diarrhea was attributed to irinotecan and the other was a result of *Clostridium difficile* infection.

As noted, 12 patients completed all six cycles of the treatment regimen. Thirty-one patients (67.4%) were taken off the study as a result of disease progression. Two patients (4.3%) experienced significant adverse effects that led to their being taken off the study, and only one patient voluntarily withdrew participation from the study after experiencing *C. difficile* infection.

All 46 patients enrolled were evaluated for response. Four patients had a partial response (PR), for an overall objective response rate of 8.7% (95% confidence interval [CI], 3.4–20.3%). Three of the partial responses were observed in the first 18 patients enrolled on the study. No complete responses were observed. Seventeen patients (37.0%) had disease stabilization as their best response. The clinical benefit rate (PR + SD) was 45.7% for the entire cohort.

Nine patients (19.6%) had stable and treated brain metastasis at the time of enrollment. None of these patients developed clinical progression of their previously treated brain metastases or new central nervous system (CNS) metastasis while on the study. Three patients (6.5%) without prior brain metastasis developed new brain parenchymal metastasis while on the study.

Intent-to-treat median time to progression was 1.8 months (95% CI, 1.5–3 months) as shown in Figure 1. At the time of last follow-up in May of 2005, the intent-to-treat median overall survival was 9.8 months (95% CI, 4.3–12.8 months). The Kaplan-Meier survival curve is shown is Figure 2. One-year overall survival rate was 34% (96% CI, 20–48.7%).

Information on the subsequent therapy or sequelae after completing the study was available for only 37 patients (80%). On completion of the study, 15 patients (32%) did not receive any subsequent therapy and were referred for hospice care. As detailed below, one patient (2%) died unexpectedly while on the study. Thirteen patients (28%) subsequently received an epidermal growth factor receptor tyrosine kinase inhibitor, either gefitinib or erlotinib, and eight patients (17%) received third-line cytotoxic chemotherapy, which included single-agent gemcitabine, vinorelbine, or docetaxel.

Toxicity

The combination of temozolomide and irinotecan was generally well tolerated (Table 3). The majority of toxicities were mild (grade 1–2). During the course of the study, one patient died unexpectedly during cycle 2, day 16, possibly related to the treatment regimen. *Pneumocystis jiroveci* pneumonia occurred in one patient who was not taking corticosteroids. Two patients were taken off the study as a result of intolerance to the regimen. Both of those patients developed severe nausea, diarrhea, and dehydration after one and two cycles of therapy, respectively. The major toxicities are listed in Table 3.

TABLE 2. Response to Therapy and Survival

	Value
Median No. of cycles	2
Reason for discontinuation	
Completed six total cycles	12 (26.1)
Disease progression/death	31 (67.4)
Adverse effects	2 (4.3)
Withdrew consent	1 (2.2)
Response	
Complete response	0 (0.0)
Partial response	4 (8.7)
Stable disease	17 (37.0)
Progressive disease	25 (54.3)
Median time to progression (mo)	1.8
Median survival (mo)	9.8
One-year survival	34%

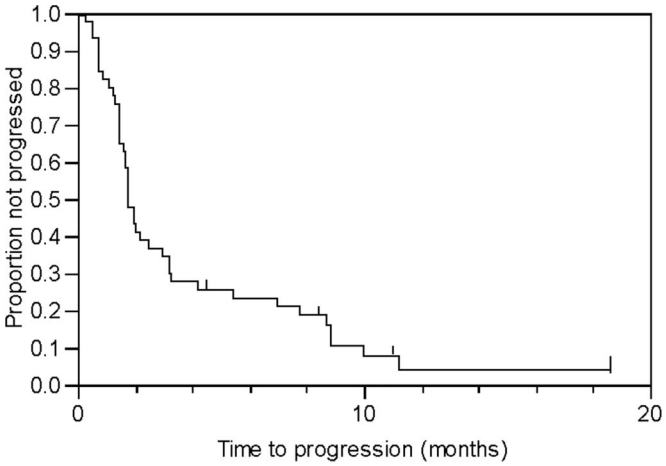

FIGURE 1. Progression-free survival for all patients enrolled in the study of temozolomide/irinotecan ($n = 46$). *Bars* indicate censored patients.

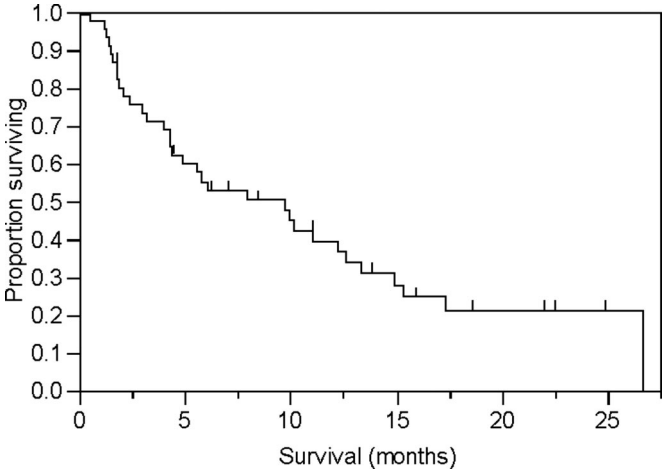

FIGURE 2. Overall survival for all patients enrolled in the study of temozolomide/irinotecan ($n = 46$). Survival time was calculated from the date on which patients were entered into the study. *Bars* indicate censored patients.

TABLE 3. Major Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Hematologic toxicities					
Anemia	18	10	1	0	29 (63.0)
Leukopenia	6	8	4	0	18 (39.1)
Lymphopenia	1	9	3	0	13 (28.3)
Neutropenia	2	7	1	0	10 (21.7)
Thrombocytopenia	2	0	2	0	4 (8.7)
Nonhematologic toxicities					
Fatigue	19	10	3	1	33 (71.7)
Pain	15	10	3	0	28 (60.9)
Nausea	16	8	3	0	27 (58.7)
Diarrhea	15	5	4	0	24 (52.2)
Hyperglycemia	13	6	1	0	20 (43.5)
Vomiting	10	7	2	0	19 (41.3)
Anorexia	11	7	0	0	18 (39.1)
Constipation	13	1	1	0	15 (32.6)
Hyponatremia	11	0	2	0	13 (28.3)
Hypoalbuminemia	6	5	1	0	12 (26.1)
Alopecia	5	7	0	0	12 (26.1)

Hematologic Toxicity

No grade 4 hematologic toxicities were seen. In general, most hematologic toxicities were mild (grade 1 or 2). Mild anemia was the predominant hematologic toxicity observed, accounting for 63%.

Leukopenia, lymphopenia, and neutropenia occurred in approximately 39%, 28%, and 22% of patients, respectively. Six episodes of febrile neutropenia were observed in four patients. In two of these patients, febrile neutropenia occurred in cycle 5, leading to dose reduction. One other patient who developed febrile neutropenia was intolerant of the regimen secondary to nausea, vomiting, and diarrhea and was taken off the study after only one cycle. The remaining patient with febrile neutropenia developed febrile neutropenia in cycle 1 and again in cycle 2 despite a dose reduction.

Nonhematologic Toxicity

Fatigue was the predominant toxicity, occurring in more than 70% of patients. Most cases of fatigue were mild. There was only one episode of grade 4 fatigue observed in the study where the patient had clinical disease progression after one cycle.

Diarrhea was observed in more than 50% of patients but was generally mild. Of four patients with grade 3 diarrhea, one patient was taken off the study after developing severe diarrhea in cycle 1, whereas the other three patients tolerated a reduced dose of irinotecan in subsequent cycles.

Nausea and vomiting were commonly observed, occurring in up to 59% and 41% of patients, respectively. Only approximately 10% of the cases of nausea and vomiting were grade 3. Nausea and vomiting arising from this regimen were easily managed and prevented with standard antiemetics.

DISCUSSION

In this study, we demonstrated that the combination has activity as a second-line combination regimen in NSCLC. The response rate of 8.7% and disease control rate (PR + SD) of 45.7% appears similar to that of single-agent docetaxel[3] or pemetrexed.[4] For our regimen, the median number of treatment cycles was two and median time to progression was 1.8 months, compared with single-agent docetaxel or pemetrexed, where the median number of treatment cycles was four and the median time to progression was approximately 3 months.[4] However, the median overall survival of 9.8 months and the 1-year overall survival rate of 34% are comparable to those of other standard second-line therapies.[4,5]

Approximately 30 to 40% of NSCLC patients develop brain metastasis.[6,7] This results in significant morbidity as a result of the metastasis itself and treatment-related toxicities. Brain metastases from a variety of solid tumors including NSCLC have been responsive to temozolomide administered as monotherapy.[13,14] In addition, recent data have shown that 6 months of adjuvant temozolomide was associated with a survival advantage in patients with surgically resected glioblastoma.[42] In our study, three patients without prior known CNS lesions developed brain metastasis while on the study. However, patients who had treated brain metastasis before receiving temozolomide/irinotecan did not develop new lesions in the CNS clinically. This suggests that temozolomide has little role in prophylaxis against brain metastasis in NSCLC. Conversely, in trials evaluating second-line therapies in NSCLC, the sites of treatment failure in particular CNS metastasis are not well described. Furthermore, because the median duration of therapy was only two cycles, there may have been preexisting asymptomatic brain metastasis before the initiation of the study in the patients who were found to have brain metastasis. Because patients on the study were not required to undergo head computed tomographic evaluation unless deemed clinically necessary, the study does not address the role of temozolomide in preventing recurrence in previously irradiated or resected CNS sites.

CONCLUSION

In conclusion, we showed that temozolomide and irinotecan is a modestly active second-line regimen in NSCLC. However, the response rate of approximately 9% demonstrated in the current trial is consistent with our null hypothesis. The toxicity profile of temozolomide and irinotecan was favorable and most toxicities were mild (grade 1 or 2). Given the availability of other currently approved agents in the second-line treatment setting for NSCLC, this combination does not warrant further investigations as studied here.

ACKNOWLEDGMENTS

This study was supported by Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough Corporation, and by University of Chicago Cancer Research Center grant 20021431. We would like to thank Harvey Golomb, M.D., Ravi Salgia, M.D., Ph.D., Patrick Ma, M.D., M.Sc., Ezra Cohen, M.D., hematology-oncology fellows, and patients and their families for participating in the study. We thank DeZheng Hou and Kurombi Wade-Oliver for statistical analysis and data management.

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